Docket No.: GEN 3.0-015

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Kamalakar TALASILA et al.	:	
Application No.: 10/510,064	:	Group Art Unit: 1625
Filed: February 13, 2006	:	Examiner: Chang, Celia C.
For: ANTIHISTAMINE DECONGESTANT COMPOSITIONS	:	
_____ X		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

BRIEF ON APPEAL

Further to the Notice of Appeal that was filed on May 19, 2010 for the subject application, a brief in support of the appeal is now submitted. Submission of a brief in support of the appeal is due by July 19, 2010. Accordingly, this brief is being timely filed.

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REAL PARTY IN INTEREST

The real parties in interest are Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories, Inc., assignees of the inventors' rights in the instant application.

RELATED APPEALS AND INTERFERENCES

The undersigned is not aware of any appeals or interferences that are related to this appeal, or which will affect or have a bearing on this appeal.

STATUS OF CLAIMS

Claims 18-37 were finally rejected in an Office Action mailed on February 19, 2010 ("the Final Office Action"), and are the subject of this appeal. Claims 1-17 were previously canceled.

STATUS OF AMENDMENTS

No claims have been amended, added or cancelled following the Final Office Action.

SUMMARY OF CLAIMED SUBJECT MATTER

The claimed subject matter encompasses pharmaceutical compositions.

Independent claim 18 is directed to a pharmaceutical composition comprising:

a) a tablet layer comprising an antihistaminic drug, a cellulose derivative, a polyol, a starch derivative, and a disintegrant; *(Example 1, Step A: Formulation (A))* and

b) a tablet layer comprising a decongestant drug and a sustained release compound. *(Example 1, Step B: Formulation (B))*

Independent claim 27 is directed to a pharmaceutical composition comprising:

a) a tablet layer comprising an antihistaminic drug, cellulose, mannitol, starch, and croscarmellose sodium; *(Example 1, Step A: Formulation (A))* and

b) a tablet layer comprising a decongestant drug and a mixture of polyvinyl acetate and povidone. *(Example 1, Step B: Formulation (B))*

Independent claim 37 is directed to a pharmaceutical composition comprising:

a) a tablet layer comprising crystalline form X of fexofenadine hydrochloride, about 20 to about 45

percent by weight cellulose, about 10 to about 30 percent by weight mannitol, about 5 to about 25 percent by weight starch, and about 4 to about 15 percent by weight of a disintegrant; *(Example 1, Step A: Formulation (A))* and

b) a tablet layer comprising a salt of pseudoephedrine and about 40 to about 80 percent by weight of a mixture comprising about 80 percent polyvinyl acetate and about 19 percent povidone. *(Example 1, Step B: Formulation (B))*

The dependent claims are directed to various embodiments of the disclosed pharmaceutical compositions.

A copy of the appealed claims is appended hereto, beginning on page 21.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether claims 37 and 18-36 reading thereon are invalid under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

II. Whether claims 37 and 18-36 reading thereon are unpatentable under 35 U.S.C. § 103(a) over U.S. Patent 6,039,974 to MacLaren et al. ("MacLaren"), in view of *Pharmapedia*, 2009 ("Pharmapedia") or Ahjel, 2008 ("Ahjel"), and further in view of U.S. Patent 6,210,712 to Edgren et al. ("Edgren") and Buhler, 2009 ("Buhler").

ARGUMENT

I. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 37, and 18-36 reading on claim 37, stand finally rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. According to the Examiner in the final Office Action, the specification lacks enablement as to how the crystalline Form X can be prepared into a composition which can maintain the particular crystalline structure (claimed limitation) without the allegedly conventional recognized conversion to its thermodynamic form. The Examiner maintains that mixing fexofenadine hydrochloride Form X with isopropyl alcohol to obtain a desired wet mass, as taught in the subject application, would dissolve the crystalline fexofenadine hydrochloride, as allegedly evidenced in U.S. Patent Application Publication 2005/0256163.

Appellants maintains that claims 37 and 18-36 reading on claim 37 satisfy the enablement requirement under 35 U.S.C. § 112, first paragraph. To satisfy the enablement requirement, the patent specification must contain sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. *See* MPEP § 2163.01. The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used

in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *See* MPEP § 2164.04.

The Examiner apparently believes that the process used in Example 1 of the subject application, wherein the dry mixture from the granulator is mixed with isopropanol to obtain a "desired wet mass," would dissolve the fexofenadine hydrochloride Form X into the amorphous form. The Examiner relied on US 2005/0256163 for evidence of this transformation.

However, as explained in Appellants' previous submission, US 2005/0256163 actually teaches a preparation of ***bulk*** fexofenadine hydrochloride Form XVI comprising, *inter alia*, dissolution of ***fexofenadine base*** in isopropanol. As such, US 2005/0256163 has no relevance to the extent ***granulated*** crystalline ***fexofenadine HCl*** might dissolve in isopropanol.

The Examiner stated in the final Office Action that this allegation of irrelevance is misleading and incorrect because a solution containing an acid and a free base forms a salt *in situ*. However, as recognized by the Examiner, fexofenadine hydrochloride Form XVI ***precipitated out*** of the isopropanol solution in US 2005/0256163. There is no indication that the opposite occurs, namely that fexofenadine hydrochloride Form XVI fully dissolves in isopropanol, as the Examiner alleges.

Also, as explained Appellants' previous submission, the Examiner ignored the teaching in the instant application that isopropanol is added to the dry mix to

obtain a "desired wet mass," which is then dried in fluidized bed drier. *See* page 10, lines 16-18. As one of skill in the art recognizes, obtaining a "desired wet mass" is not equivalent to "dissolution." The Examiner has provided no evidence that the addition of isopropanol to granulated crystalline fexofenadine hydrochloride to achieve a "desired wet mass" results in complete dissolution and loss of all crystalline form. Indeed, earlier patent literature teaches that various polymorphic forms of fexofenadine hydrochloride could be wet granulated with no evidence of loss of crystalline structure. *See, e.g.*, U.S. Patent 5,738,872, col. 14, lines 43-62. Again, to the extent any fexofenadine hydrochloride is dissolved into amorphous form, that portion would be outside the scope of the claims. *See Ex parte Li*, Appeal No. 2007-1348, for U.S. Patent Application No. 10/650,253, at 9 (BPAI 2007) ("A mixture of (1) azithromycin, resulting from de-crystallization of form F when placed in water, and (2) water are not covered by, and do not fall within the scope of claim 125."); *Ex parte Glover*, Appeal No. 2006-2861, for U.S Patent Application No. 10/007,272, at 5 (BPAI 2007) ("[T]he claimed invention differs from the disclosure of Chamberlain in that the claims specifically recite a *crystalline* form of the compound. The rejection improperly ignores this element of the claims.") (emphasis in original).

Furthermore, even if in some embodiments of fexofenadine hydrochloride within the scope of the examined subject matter did truly lose all crystallinity, the compositions defined by the claims would still be useful, since it is not disputed that the specification teaches how to make and use pharmaceutical compositions comprising fexofenadine hydrochloride Form X. *See Li*, *supra* ("Even if we

assume that some embodiments within the scope of claim 125 might be non-enabled, the composition defined by claim 125 would still be useful and the specification otherwise advises one skilled in the art how to make and use substantially pure [crystalline] azithromycin Form F mixed with other carriers and diluents.").

Appellants further point out that one having skill in this art would be able to determine, such as using X-ray diffraction techniques, whether a pharmaceutical formulation or mixture being processed into a pharmaceutical formulation contains fexofenadine hydrochloride Form X, making possible a ready determination of whether the claim is being infringed.

The Examiner also apparently believes that processing crystalline fexofenadine hydrochloride Form X into a pharmaceutical dosage form could result in the transformation into a different crystalline form. However, as explained in Appellants' previous submission, nothing in the examined subject matter requires that crystalline Form X be maintained indefinitely in the composition, or that it even be the only form present in the composition, and it is error for the Examiner to read such limitations into the claims. Appellants specifically provide examples showing the preparation of pharmaceutical compositions comprising crystalline fexofenadine hydrochloride Form X, thereby adequately describing and enabling the examined subject matter. *See Ex parte Reddy*, Appeal No. 2009-000439, for U.S. Patent Application No. 10/505,826, at 23 (BPAI 2009) ("[B]ecause the Specification lists the solid formulations and excipients suitable for the crystalline forms X and Y we agree . . . that a person of

ordinary skill in the art would have understood Appellants to be in possession of the [claimed] subject matter . . . [and] that any experimentation that would be required to prepare the claimed pharmaceutical compositions would be routine in nature, rather than undue."). In fact, the instant specification specifically teaches that "polymorphic conversion is most common still challenging product quality," but that the examples are "robust enough to assure the product quality characteristics in routine manufacturing." *See* page 9, line 35 to page 6, line 6. The Examiner cited no direct evidence to the contrary, or any reason to doubt the objective truth of these statements. *See Reddy*, *supra* ("While it may be true that polymorphic forms can undergo undesirable changes when formulated into dosage forms, the Examiner has not explained . . . why the *claimed* crystalline forms would be subject to these problems.") (emphasis in original).

The references relied on by the Examiner during the instant prosecution actually support the conclusion that the examined subject matter is enabled, the specification providing guidance to one of skill in the art of pharmaceutical formulations. *See Reddy*, *supra* ("If anything, the disclosures cited by the Examiner suggest that a skilled artisan knew what actions to avoid when formulating sensitive polymorphic forms, and if encountering problems, what actions might be taken to rectify them.") Furthermore, several of the references cited by the Examiner explain that polymorphic transformation can be very slow (on the order of years) owing to the relative stability of the metastable form. For example, Muzaffar notes at page 60:

> When the rate of conversion of a metastable form is so slow as to be negligible, the solubility of the

> compound will be maximal and will have a faster rate of dissolution and hence absorption. This biopharmaceutical property of the polymorphs could be explained for achieving better results in the formulation of drugs, especially in the unit dosage forms of the drugs.

Thus, even assuming that fexofenadine hydrochloride Form X would be subject to polymorphic conversion (mere conjecture at this point), its possible transformation at some point in the future does not detract from its utility while in the claimed form. Again, any fexofenadine hydrochloride not having the Form X crystal structure would be outside the scope of the claims. As MPEP § 2164.01(b) states:

> Naturally, for unstable and transitory chemical intermediates, the "how to make" requirement does not require that the applicant teach how to make the claimed product in stable, permanent or isolatable form. *In re Breslow*, 616 F.2d 516, 521, 205 USPQ 221, 226 (CCPA 1980).

Since the specification teaches how to make and use pharmaceutical compositions containing fexofenadine hydrochloride Form X, Appellants maintain that claims 37 and 18-36 reading thereon satisfy the enablement requirement, and reversal of the rejection is respectfully requested.

II. Rejection Under 35 U.S.C. § 103

Claims 37 and 18-36 reading on claim 37 stand finally rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over MacLaren in view of Pharmapedia or Ahjel, further in view of Edgren and Buhler. According to the Examiner in the final Office Action, MacLaren discloses bilayer compositions

containing a layer of antihistamine fexofenadine in immediate release formulation and a layer of pseudoephedrine in sustained release formulation. The Examiner acknowledged that MacLaren does not disclose mannitol, but asserts that Pharmapedia or Ahjel teach that mannitol and lactose are optional choices of diluent. The Examiner also acknowledged that MacLaren does not disclose pyrrolidone and vinyl acetate, but asserted that Edgren and Buhler teach pyrrolidone and vinyl acetate for sustained release.

In rejecting claims under 35 U.S.C. § 103, it is incumbent upon the Examiner to establish a factual basis to support the legal conclusion of obviousness. *See In re Fine*, 837 F.2d 1071, 1073 (Fed. Cir. 1988). In so doing, the Examiner must make the factual determinations set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), *viz.*, (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the art. "[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Furthermore, although the analysis need not identify explicit teachings directed to the claimed subject matter, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). As such, "'there must be some

articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *Id.* (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

The § 103 rejection is based primarily on the Examiner's mistaken belief, discussed above, that the instant specification fails to adequately describe and enable pharmaceutical compositions comprising fexofenadine hydrochloride Form X. Specifically, the Examiner states that elected active ingredient, fexofenadine hydrochloride Form X, in its dissolved form, would read on the compositions disclosed in MacLaren.

However, as discussed above with respect to the enablement rejection, no evidence has been provided to support the conclusion that the addition of isopropanol to granulated crystalline fexofenadine hydrochloride Form X to achieve a "desired wet mass" results in complete dissolution and loss of all crystallinity. As noted above, earlier patent literature teaches that various polymorphic forms of fexofenadine hydrochloride could be wet granulated with no evidence of loss of crystalline structure. Reading MacLaren to cover the claimed composition improperly ignores a critical limitation of the examined subject matter, namely that the fexofenadine hydrochloride be crystalline Form X. *See Glover*, *supra* ("[T]he claimed invention differs from the disclosure of Chamberlain in that the claims specifically recite a *crystalline* form of the compound. The rejection improperly ignores this element of the claims.") (emphasis in original). Also, nothing in the examined subject matter requires that crystalline Form X be maintained indefinitely in the composition, or that it even be

the only form present in the composition. Again, to the extent any fexofenadine hydrochloride is dissolved into amorphous form, that portion is outside the scope of the claims. *See Li, supra* ("A mixture of (1) azithromycin, resulting from de-crystallization of form F when placed in water, and (2) water are not covered by, and do not fall within the scope of claim 125.").

Furthermore, as explained in Appellants' previous submission, MacLaren's recitation of fexofenadine hydrochloride would not have suggested the specific crystalline form under examination. Although the polymorphic nature of fexofenadine hydrochloride is known, nothing in MacLaren, or the art in general relied on by the Examiner, would have suggested fexofenadine hydrochloride Form X, or a method for its preparation. The mere existence of other polymorphs is not sufficient to support a *prima facie* case of obviousness under these circumstances – the prior art must suggest the ***specific*** polymorph that is claimed. *See Bristol-Myers Co. v. U.S. Int'l Trade Comm'n*, 892 F.2d 1050, 1989 WL 147230 (Fed. Cir. Dec. 8, 1989) (unpublished decision) ("The law of § 103 requires quite a different inquiry from that conducted by the ALJ. The correct inquiry is not whether the Bouzard monohydrate [polymorph] could have been produced by manipulation of other cefadroxil processes, once the existence of the Bouzard monohydrate was known. The question is whether it would have been obvious to ***make the Bouzard monohydrate, based on the prior art***.") (emphasis added); *Ex parte Reddy*, Appeal No. 2009-002678, for U.S. Patent Application No. 10/816,798, at 8 (BPAI 2009) ("The other references cited by the Examiner disclose that many pharmaceutical compounds exhibit polymorphism

and can exist as more than one crystalline form. However, the Examiner has pointed to no disclosures in the prior art that support a conclusion that the cited references would have suggested the ***specific crystal form*** of Donepazil hydrochloride that is claimed.") (emphasis added); *Ex parte Havens*, Appeal No. 2001-0091, for U.S. Patent Application No. 08/732,254, at 6 (BPAI 2001) ("The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the ***specific S and T crystal forms*** that are the subject of the instant claims.") (emphasis added).

Since none of the references relied on by the Examiner would have suggested fexofenadine hydrochloride Form X, or a method for its preparation, Appellants maintain that claims 37 and 18-36 reading thereon are not unpatentable over MacLaren, in view of Pharmapedia or Ahjel, further in view of Edgren and Buhler, and reversal of the rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Appellants maintain that claims 18-37 meet the requirements for patentability under 35 U.S.C. §§ 101 *et seq.* Accordingly, reversal of the Examiner's rejections is appropriate and is respectfully solicited.

Date: July 19, 2010

Respectfully submitted,

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CLAIMS APPENDIX

18. A pharmaceutical composition comprising:

a) a tablet layer comprising an antihistaminic drug, a cellulose derivative, a polyol, a starch derivative, and a disintegrant; and

b) a tablet layer comprising a decongestant drug and a sustained release compound.

19. The pharmaceutical composition of claim 18, wherein an antihistaminic drug comprises crystalline Form X of fexofenadine hydrochloride.

20. The pharmaceutical composition of claim 18, wherein a cellulose derivative comprises powdered cellulose, microcrystalline cellulose, or a mixture thereof.

21. The pharmaceutical composition of claim 18, wherein a polyol comprises mannitol, xylitol, or a mixture thereof.

22. The pharmaceutical composition of claim 18, wherein a starch derivative comprises corn starch, potato starch, starch 155, or a mixture of any two or more thereof.

23. The pharmaceutical composition of claim 18, wherein a disintegrant comprises sodium starch glycolate, sodium carboxymethylcellulose, crosslinked

polyvinylpyrrolidone, croscarmellose sodium, or a mixture of any two or more thereof.

24. The pharmaceutical composition of claim 18, wherein a decongestant drug comprises pseudoephedrine, phenylephrine, phenylpropanolamine, a pharmaceutically acceptable salt of any of the foregoing, or a mixture of any two or more thereof.

25. The pharmaceutical composition of claim 18, wherein a sustained release compound comprises: a mixture comprising polyvinyl acetate and povidone; sodium alginate; xanthan gum; carbopol; chitosan; ethyl cellulose; a cellulose ether; a methacrylic polymer; or a mixture of any two or more thereof.

26. The pharmaceutical composition of claim 18, wherein an antihistaminic drug comprises crystalline form X of fexofenadine hydrochloride and a decongestant drug comprises pseudoephedrine or a salt thereof.

27. A pharmaceutical composition comprising:

a) a tablet layer comprising an antihistaminic drug, cellulose, mannitol, starch, and croscarmellose sodium; and

b) a tablet layer comprising a decongestant drug and a mixture of polyvinyl acetate and povidone.

28. The pharmaceutical composition of claim 27, wherein an antihistaminic drug comprises crystalline form X of fexofenadine hydrochloride.

29. The pharmaceutical composition of claim 27, wherein a decongestant drug comprises a salt of pseudoephedrine.

30. The pharmaceutical composition of claim 27, wherein tablet layer a) comprises about 20 to about 45 percent by weight cellulose.

31. The pharmaceutical composition of claim 27, wherein tablet layer a) comprises about 10 to about 30 percent by weight mannitol.

32. The pharmaceutical composition of claim 27, wherein tablet layer a) comprises about 5 to about 25 percent by weight starch.

33. The pharmaceutical composition of claim 27, wherein tablet layer a) comprises about 4 to about 15 percent by weight croscarmellose sodium.

34. The pharmaceutical composition of claim 27, wherein tablet layer b) comprises about 40 to about 80 percent by weight of a mixture of polyvinyl acetate and povidone.

35. The pharmaceutical composition of claim 27, wherein tablet layer b) comprises about 40 to about 80 percent by weight of a mixture comprising about 80 percent polyvinyl acetate and about 19 percent povidone.

36. The pharmaceutical composition of claim 27, wherein tablet layer b) is formed by compressing granules comprising a decongestant drug and a mixture of polyvinyl acetate and povidone, about 5-15 percent of the granules being retained on an 80 mesh sieve, about 10-25 percent of the granules being retained on a 100 mesh sieve, and about 80-95 percent of the granules being retained on a 200 mesh sieve.

37. A pharmaceutical composition comprising:

a) a tablet layer comprising crystalline form X of fexofenadine hydrochloride, about 20 to about 45 percent by weight cellulose, about 10 to about 30 percent by weight mannitol, about 5 to about 25 percent by weight starch, and about 4 to about 15 percent by weight of a disintegrant; and

b) a tablet layer comprising a salt of pseudoephedrine and about 40 to about 80 percent by weight of a mixture comprising about 80 percent polyvinyl acetate and about 19 percent povidone.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.